REMARKS

Status of the Claims

Claims 64, 65, 68-70, 72, 74, 75, 91-103, 132, 145, 147, 148 and 150-174 are in the application.

Claims 64, 65, 68-70, 72, 74, 75, 91-103, 132, 145, 147, 148 and 150-174 were rejected.

By way of this amendment, claims 169 and 170 have been amended.

Upon entry of this amendment, claims 64, 65, 68-70, 72, 74, 75, 91-103, 132, 145, 147, 148 and 150-174 will be pending.

Summary of the Amendment

Claims 169 and 170 have been amended to recite that the ligand or the antibody is unconjugated. Support for this amendment can be found throughout the specification and the as-filed claims.

No new matter has been added.

Claim Rejections under 35 USC § 112, First Paragraph

Claims 64, 65, 68-70, 72, 74, 75, 91-103, 132, 145, 147-148, and 150-174 stand rejected under 35 U.S.C. § 112, first paragraph for allegedly not being enabling for the full scope of the claim. The Office alleges that the while being enabling for an anti-guanylyl cyclase C antibody or a guanylyl cyclase C binding fragment thereof conjugated to a therapeutic agent, the present application is allegedly not enabled where the antibody or a guanylyl cyclase C binding fragment thereof is not conjugated to a therapeutic agent. The Office also alleges that the claims are not enabled for a method of inducing a cytostatic effect comprising the steps and doses recited in the presently claimed invention. The Office also alleges that the claims are not enabled for the recited doses and time periods for sustaining the doses. The Office alleges that "one cannot extrapolate the teachings of the specification the enablement of the scope of the claims because no nexus has been established between the unconjugated ligands to [GCC] and inducing a cytostatic effect or killing in primary or metastasized" cancer cells. (Office Action , page 7).

The Office also alleges that the specification does not discuss what treatment protocol will maintain a concentration greater than or equal to the EC50 of the unconjugated ligand for at least 15 days or at least 30 days or an amount sufficient to maintain a concentration greater than or equal to 10 times the EC50 of the GCC ligand. Therefore, the Office alleges that the claims would require undue experimentation. Applicants respectfully disagree.

The presently claimed invention is enabled because one of skill in the art would not need to be use undue experimentation to practice the claimed invention. The Office alleges that "other than uroguanylin, the art does not teach that unconjugated GCC ligands can treat primary or metastasized colorectal cancer and the development of therapeutics for malignant disorders such as colorectal cancer is well known in the art to be unpredictable." (Office Action, page 8). The Office cites Gura (Science, 1997, 278:1041-1042) as evidence of the unpredictability. The Office, however, has not provided any reasonable evidence to question the enablement of the presently claimed invention. There is nothing in the references cited by the Office that supports a reasonable basis to question the enablement of the presently claimed invention. As Applicant has previously stated, and is repeated here, the Office is analogizing the approval of a drug with patentability. This is not the correct standard.

As evidence the Office is not using the correct standard, the Office states, that "many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy." (Office Action, page 8). Applicant respectfully asserts that the number that have been shown to be approved by the FDA (39) is not relevant to enablement and patentability. The standards for drug approval are vastly different from patentability. The Office uses these numbers to show that the art is unpredictable. In contrast, however, the numbers show that once a class of molecules is identified as having activity, one of skill in the art can predict whether or not it will have activity without undue experimentation. One of skill in the art may not be able to predict whether a compound or class of compounds may be approved by the FDA for marketing, but marketing approval requires more than simply showing a drug is effective. FDA approval requires a determination of safety

and efficacy and compares that balance to acceptable risk depending on a given condition. The enablement requirement for patentability is less comprehensive and requires determining whether one of skill in the art would accept Applicant's assertions that the claims are enabled. Additionally, there are other non-scientific reasons as to why a compound may not be brought to market including, but not limited to, not being able to recoup the investment. The fact that a compound is not brought to market or approved by the FDA is not relevant to the enablement analysis.

The Office throughout the application makes the same error when it determines predictability based upon marketing approval. Marketing approval does not determine patentability. Rather, it is whether one of skill in the art can practice the claimed invention without undue experimentation. Undue experimentation is viewed based upon what is taught in the specification and the knowledge of the skilled artisan. Here, one of skill in the art can follow the specification without undue experimentation. Based upon the specification the skilled artisan can identify the type of ligand to use, determine its EC50 and adjust the dose accordingly so that the ligand concentration and dosage amount is within the scope of the claim. Applicant is not required to explicitly recite each and every step of the protocol when the protocol can be performed without undue experimentation. The Office has failed to establish that one of ordinary skill in the art would doubt the assertions of enablement.

As the M.P.E.P. explains, "in order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. (M.P.E.P. § 2164.04, citing *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)) "It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *In re Marzocchi* 439 F.2d at 224, 169 USPQ at 370 (CCPA 1971). The Office has not put forward any evidence other than evidence that only a small number of compounds gain FDA marketing approval to treat cancer. This standard,

however, is not the standard for patentability. The Office has not met its burden. Therefore, because the Office has not met its burden, the rejection under 35 U.S.C. § 112, first paragraph, must be withdrawn.

The presently claimed invention is directed to various methods. The cited references demonstrate the methods, such as those presently claimed, are not unpredictable to the point where undue experimentation would be required. Whether the presently claimed methods are sufficient to gain FDA marketing approval is an unrelated and separate issue (see discussion above). The Office's citation of Young *et al.* (U.S. Patent Application No. 2004/0180002) does not support the Office's rejection. In contrast, Young supports that conclusion that the presently claimed invention is enabled. Young describes an antibody that can halt tumor progression. Young also refers to clinical trial data where success in at least one patient was also shown. These results do not show that the methods are not enabled, but rather that one of skill in the art would understand that nothing more than following the specification and, at most, routine experimentation would be required to practice the presently claimed methods. Predictability of FDA approval for marketing a therapeutic is not required to satisfy the enablement requirement.

The Office also alleges that it would not have been predicable to maintain a concentration as recited in the claims. The Office provides no evidence other than generalized conclusions that the ligands "may be degraded *in vivo* before achieving the claimed concentrations." The standard used by the Office is not sufficient to shift the burden. The Office cites Wolfe *et al.* (The J. of Nuclear Medicine, March 2002, 43:392-399) to allege that because GCC ligand is cleared from the blood by urinary excretion then one of skill in the art would not be able to maintain the dose as recited in the claims. However, Wolfe does not state that the dose cannot be maintained or it would require undue experimentation. Wolfe describes *in vivo* imaging of human colon cancer xenografts in immunodeficient mice using a GCC specific ligand. Wolfe reports the kinetic of various ligands, but nowhere does Wolfe state that a certain concentration could not be maintained. One of skill in the art would know or be able to determine without undue experimentation the kinetics of the ligand and adjust, without undue experimentation, the

protocol accordingly to maintain the presently claimed concentrations. There is nothing in Wolfe or any of the other cited references that says undue experimentation would be required to maintain the current concentrations and durations of administration.

The Office admits that its evidence is lacking by stating that even if the concentrations could be maintained that the amounts may not be tolerable. The Office alleges that one of skill in the art could not practice the claimed invention without undue experimentation without guidance and direction to the effect of the method on kidney function and sodium homeostasis. (Office Action, page 11). As the Office has done throughout the Office Action, here the Office has substituted its role for the role of the FDA. The Office's role is not concerned with whether or not the presently claimed method may affect the kidneys. All treatments have risk/reward profiles and it is the FDA's role, not the USPTO's role, to make the determination as to whether or not the risk/reward balance is sufficient to allow marketing of a drug. Patentability is not concerned with risk/reward.

The Office also alleges that there is no evidence that the presently claimed invention will work with unconjugated ligands or antibodies. The Office, however, has not provided sufficient evidence to suggest that the presently claimed invention is not enabled. The Office cites Taber's Cyclopedic Medical Dictionary to show that different cancers have different genetic profiles. However, the reference has no discussion about GCC expression and the cancers recited in the claims. The Office has provided no evidence to question what is stated in the specification. The Office instead cites very general references throughout the Office Action to allege that the claims are not enabled, but these references are not sufficient to question the enablement of the presently claimed invention. None of the references (alone or in combination) cited by the Office are sufficient to question the enablement of the presently claimed invention. Therefore, the Office has failed to carry its burden to show that the claims are not enabled.

In contrast to the Office's rejection, the specification provides how to administer the ligand and at what concentrations. For examples, paragraphs 128-136 explain and describe how to administer the compositions in the presently claimed methods. One of skill in the art can

follow the specification without having to perform undue experimentation. None of the references cited by the Office contradict the present specification and none of the references establish a reasonable basis to question the enablement of the present claimed invention. Accordingly, the claims are enabled.

Other evidence showing that the claims are enabled is provided in Pitari *et al* (Cancer Research 2005, Vol. 65: 23 December 1, 2005, attached hereto). Pitari discusses the interruption of homologous desensitization in cyclic guanosine 3',5'-monophosphate signaling restores colon cancer cytostasis by bacterial enterotoxins. Pitari reports that colon cancer cells undergo cytostasis in the absence of checkpoint arrest or apoptosis when exposed to heat-stable enterotoxins. (see, Pitari, p. 11130, right column and Figure 1A). The paper further describes the resistance to cytostasis, but also describes the way in which the resistance can be overcome. The protocol described in the Pitari reference is similar to what is disclosed in the present application and is presently claimed. A cancer cell is contacted with an unconjugated GCC ligand with a cytostatically effective amount of the ligand and cytostasis is induced. Therefore, this evidence along with the present specification demonstrates that the presently claimed invention is enabled and can be practiced without undue experimentation. This paper and the present specification demonstrate that a sustained dosage, as is recited in the claims, can be cytostatic and effective to induce a cytostatic effect, inhibit the proliferation, and/or kill the cancer cell. Accordingly, the claims are enabled.

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph alleging that the claims are not enabled be withdrawn.

Claim Rejections under 35 USC § 103

Claims 169-174 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 5,879,656 in view of Cohen (Int J. Radiat Oncol. Biol Phys, 1987, 123:251-8) in further view of Queen *et. al.* (PNAS, 1989, Vol. 86, pp. 10029-10033) and in further view of Riechmann *et al.* (Nature, Vol. 332, pp. 323-327, 1988).

Claims 169-174 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 6,767,704 (Waldman) in view of Cohen.

Applicant respectfully disagrees, but solely in order to further prosecution Applicants have amended claims 169 and 170 to recite that the ligand or the antibody is unconjugated. The combination of references cited by the Office fails to yield the presently claimed invention. The Office has failed to show that the claims are *prima facie* obvious in view of the cited references. Accordingly, the claims are not obvious.

In view of the foregoing, Applicant respectfully requests that the rejection under 35 U.S.C. § 103 be withdrawn.

Double Patenting

Claims 169-174 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 30-32, 35-38, 40-55, and 57-65 of copending Application No. 10/866,951 in view of Cohen (Int J. Radiat Oncol. Biol Phys, 1987, 123:251-8) in further view of Queen *et. al.* (PNAS, 1989, Vol. 86, pp. 10029-10033) and in further view of Riechmann *et al.* (Nature, Vol. 332, pp. 323-327, 1988).

Claims 169-174 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 5, 7, 9, 10, 15-18, 23, 28-35, 38-43, 46-50, and 53-58 of U.S. Patent No. 5,879,656 in view Cohen (Int J. Radiat Oncol. Biol Phys, 1987, 123:251-8) in further view of Queen *et. al.* (PNAS, 1989, Vol. 86, pp. 10029-10033) and in further view of Riechmann *et al.* (Nature, Vol. 332, pp. 323-327, 1988).

Claims 169-174 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 6-8 of U.S. Patent No. 6,060,037 in view U.S. Patent 5,879,656, in view Cohen (Int J. Radiat Oncol. Biol Phys, 1987, 123:251-8) in further view of Queen *et. al.* (PNAS, 1989, Vol. 86, pp. 10029-10033) and in further view of Riechmann *et al.* (Nature, Vol. 332, pp. 323-327, 1988).

Claims 169-174 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 14-16 of U.S. Patent No. 6,087,109 in

view U.S. Patent 5,879,656 in view of Cohen (Int J. Radiat Oncol. Biol Phys, 1987, 123:251-8) in further view of Queen *et. al.* (PNAS, 1989, Vol. 86, pp. 10029-10033) and in further view of Riechmann *et al.* (Nature, Vol. 332, pp. 323-327, 1988).

Applicant respectfully asserts that in view of the amendments to claims 169 and 170 the rejections under the judicially created doctrine of obviousness-type double patenting are moot.

In view of the foregoing, Applicant respectfully requests that all rejections under the judicially created doctrine of obviousness-type double patenting be withdrawn.

Conclusion

Claims 64, 65, 68-70, 72, 74, 75, 91-103, 132, 145, 147, 148 and 150-174 are in condition for allowance. A notice of allowance is earnestly solicited. Applicants invite the Examiner to contact the undersigned at 610.640.7820 to clarify any unresolved issues raised by this response.

The Commissioner is hereby authorized to charge any deficiencies of fees and credit of any overpayments to Deposit Account No. 50-0436.

Respectfully submitted,

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Attachments: Exhibit A, Pitari Reference